

## SCIENTIFIC LETTER

# Heterozygosity for the haemochromatosis mutation HFE C282Y is not a risk factor for angina

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The incidence of cardiovascular disease increases progressively with age in men and is more common in younger men than in women of similar age. The difference in incidence of cardiovascular disease between the sexes diminishes in the elderly, as the incidence of female cardiovascular disease increases with age in post-menopausal females. This pattern coincides with that of iron stores; in men iron stores increase with age, while menstrual blood loss means that pre-menopausal women have little or no storage of iron with iron only accumulating post-menopause. This link was used by Sullivan<sup>1</sup> to propose that excess iron is important to the pathogenesis of atherosclerosis. Blood donation reduces body iron stores and comparing donors and non-donors provides a way of testing this hypothesis. In two studies the incidence of heart disease was found to be reduced in male blood donors, but no such reduction was found in a later, prospective study of 38 000 health professionals<sup>2</sup> (and references therein).

Haemochromatosis is characterised by excess accumulation of iron. Most patients of European origin with genetic haemochromatosis are homozygous for the C282Y mutation of the HFE gene. This mutation is particularly common in Northern Europe where between 10–20% of the population are heterozygotes. Heterozygotes have higher transferrin saturations and may accumulate more iron than subjects lacking the mutation<sup>3</sup>; however, heterozygotes rarely accumulate the concentrations of iron associated with tissue damage in subjects with haemochromatosis who are homozygous for C282Y. However, if even small increases in tissue iron concentration promote the formation of highly reactive oxygen species and lipid peroxidation, a crucial step in atherosclerosis,<sup>4</sup> then heterozygosity for C282Y may be a risk factor for cardiac disease.

Two large surveys suggested that possession of the HFE C282Y mutation may predispose to cardiovascular disorders, cardiovascular death in women,<sup>5</sup> and acute myocardial infarction in men.<sup>6</sup> Since then a number of other studies of HFE mutations and cardiovascular disease have been reported.<sup>7</sup> These have included patients with atherosclerosis, coronary heart disease, myocardial infarction, and stroke. These were smaller studies but in all cases the 95% confidence intervals for the odds ratio include 1.0. The aim of the study reported here was to test the hypothesis that HFE C282Y is a risk factor for coronary heart disease and thereby is over-represented in patients with angina.

## METHODS

Blood samples suitable for DNA extraction were collected from 742 men with angina with a mean age of 61 years, who were resident in South Wales. They were recruited from general practice based on a history of nitrate prescriptions and were the final cohort, recruited in 1996, of a larger study,

**Table 1** HFE C282Y genotypes in male patients from general practice being treated for angina and from male blood donors aged over 50 years from South Wales

	Angina patients n = 630	Blood donors n = 774
Wild type (%)	539 (85.6)	648 (83.7)
Heterozygous (%)	87 (13.8)	123 (15.9)
Homozygous (%)	4 (0.63)	3 (0.39)

There was no significant difference between frequencies ( $\chi^2 = 1.57$ ,  $p = 0.46$ ,  $df = 2$ ).

DART2 (diet and angina randomised trial 2), evaluating the effect of diet in cardiovascular disease.<sup>8</sup>

The HFE C282Y mutation was detected by PCR and restriction enzyme digestion.<sup>9</sup> Results were obtained from 630 samples. The frequency of the mutation was compared with that found for 783 male blood donors aged over 50 years who had been tested previously.<sup>3</sup>

## RESULTS

There was no significant difference in the frequency of heterozygosity or homozygosity for HFE C282Y in the men with angina and the male blood donors (table 1). Genotype frequencies did not vary with age among patients with angina or among blood donors. In the angina patients the mean (SD) ages for the genotype groups were: wild-type 61 (7) years; heterozygotes 61 (6) years; and homozygotes 55 (6) years.

We compared mortality, coronary mortality, and morbidity in the men lacking the C282Y mutation, with those carrying the mutation over a follow up period of three years. Of the wild type patients 37 had died (6.9%) compared with three of the C282Y heterozygotes (3.4%) and none of the four patients homozygous for C282Y. These numbers are not significantly different. In the whole study<sup>8</sup> the mortality, in terms of all deaths and cardiac deaths, was measured from 3–9 years after enrolment. Of the 3114 men enrolled 525 (16.9%) died and 60% of these deaths were from cardiac problems.

## DISCUSSION

This study of over 600 men with angina indicates that possession of HFE C282Y is not a risk factor for coronary heart disease. This is of particular relevance in parts of the British Isles where the incidence of ischaemic heart disease is high and up to 20% of the population are carriers of HFE C282Y.

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# IMAGES IN CARDIOLOGY

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## Saccular aneurysm on the ascending aorta after cardiac surgery



**A** 72 year old man was referred to our hospital for surgical treatment of an aneurysm on the ascending aorta. Eleven years previously he had undergone a mechanical aortic valve replacement because of severe rheumatic aortic stenosis. The ascending aorta diameter was reported as normal at the time of aortic valve surgery and he had been doing well since then. Two months before admission to our hospital, he had experienced an episode of congestive heart failure and acute bronchitis and a computed tomographic scan of the chest revealed a dilated ascending aorta.

The patient was in New York Heart Association functional class II. Physical examination disclosed no abnormality except irregular and metallic heart sounds. Laboratory data were unremarkable. Chest radiography demonstrated slight cardiomegaly. Electrocardiography showed atrial fibrillation. Transoesophageal echocardiogram revealed normal left ventricular function, normally functioning aortic prosthesis with physiologic aortic regurgitation, mild mitral stenosis and regurgitation, and an aneurysm on the ascending aorta. Magnetic resonance imaging showed a dilatation of the ascending aorta with a sinus of Valsalva diameter of 42 mm and tubular segment diameter of 80 mm, and a large saccular aneurysm on the ascending aorta (panel A). The diagnosis was confirmed at surgery (panel B). The patient was treated by simple replacement of the supracoronary ascending aorta. Pathological findings from the resected aortic wall revealed atherosclerosis without other pathological process. The postoperative course was uneventful.

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